NTP TECHNICAL REPORT

ON THE

TOXICOLOGY AND CARCINOGENESIS

STUDIES OF

ISOBUTYRALDEHYDE

(CAS NO. 78-84-2)

IN F344/N RATS AND B6C3F$_1$ MICE

(INHALATION STUDIES)

February 1999

NATIONAL TOXICOLOGY PROGRAM
P.O. Box 12233
Research Triangle Park, NC 27709

NTP TR 472

NIH Publication No. 99-3962

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
National Institutes of Health

FOREWORD

The National Toxicology Program (NTP) is made up of four charter agencies of the U.S. Department of Health and Human Services (DHHS): the National Cancer Institute (NCI), National Institutes of Health; the National Institute of Environmental Health Sciences (NIEHS), National Institutes of Health; the National Center for Toxicological Research (NCTR), Food and Drug Administration; and the National Institute for Occupational Safety and Health (NIOSH), Centers for Disease Control. In July 1981, the Carcinogenesis Bioassay Testing Program, NCI, was transferred to the NIEHS. The NTP coordinates the relevant programs, staff, and resources from these Public Health Service agencies relating to basic and applied research and to biological assay development and validation.

The NTP develops, evaluates, and disseminates scientific information about potentially toxic and hazardous chemicals. This knowledge is used for protecting the health of the American people and for the primary prevention of disease.

The studies described in this Technical Report were performed under the direction of the NIEHS and were conducted in compliance with NTP laboratory health and safety requirements and must meet or exceed all applicable federal, state, and local health and safety regulations. Animal care and use were in accordance with the Public Health Service Policy on Humane Care and Use of Animals. The prechronic and chronic studies were conducted in compliance with Food and Drug Administration (FDA) Good Laboratory Practice Regulations, and all aspects of the chronic studies were subjected to retrospective quality assurance audits before being presented for public review.

These studies are designed and conducted to characterize and evaluate the toxicologic potential, including carcinogenic activity, of selected chemicals in laboratory animals (usually two species, rats and mice). Chemicals selected for NTP toxicology and carcinogenesis studies are chosen primarily on the bases of human exposure, level of production, and chemical structure. The interpretive conclusions presented in this Technical Report are based only on the results of these NTP studies. Extrapolation of these results to other species and quantitative risk analyses for humans require wider analyses beyond the purview of these studies. Selection *per se* is not an indicator of a chemical's carcinogenic potential.

Listings of all published NTP reports and ongoing studies are available from NTP Central Data Management, NIEHS, P.O. Box 12233, MD E1-02, Research Triangle Park, NC 27709 (919-541-3419). The Abstracts and other study information for 2-year studies are also available at the NTP's World Wide Web site: http://ntp-server.niehs.nih.gov.

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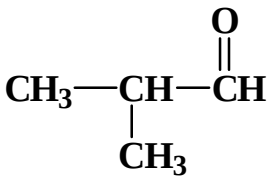
ABSTRACT



ISOBUTYRALDEHYDE

CAS No. 78-84-2

Chemical Formula: C_4H_8O Molecular Weight: 72.10

Synonyms: Dimethylacetaldehyde; 2-formylpropane; isobutanal; isobutylcarboxaldehyde; isobutyral; isobutyric aldehyde; isobutyrylaldehyde; isopropylformaldehyde; 2-methylpropanal; 2-methyl-1-propanal; α-methylpropionaldehyde; 2-methylpropionaldehyde; valine aldehyde

Isobutyraldehyde, a branched alkyl aldehyde, is used as a chemical intermediate and flavoring agent. It was nominated by the National Cancer Institute for toxicity and carcinogenicity studies by the NTP. Reasons for nomination and selection of isobutyraldehyde for study included its high potential for human exposure as suggested by its high production volume, its use as a chemical intermediate and food flavoring agent, suspicion of carcinogenicity due to an increased incidence of cancer at an aldehyde manufacturing plant where workers were exposed to a variety of aldehydes, its structural relationship to formaldehyde (a nasal carcinogen in rats), and the lack of toxicity and carcinogenicity studies on isobutyraldehyde in animals. Although human exposure occurs orally, dermally, or via inhalation, the inhalation route of exposure was selected for these animal studies because of the instability of isobutyraldehyde in water and feed. Male and female F344/N rats and B6C3F$_1$ mice were exposed to isobutyraldehyde (approximately 99% pure) by inhalation for 13 weeks or 2 years. Genetic toxicology studies were conducted *in vitro* in *Salmonella typhimurium*, L5178Y mouse lymphoma cells, and cultured Chinese hamster ovary cells; *in vivo* tests were conducted in *Drosophila melanogaster* germ cells and bone marrow cells of rats and mice.

13-WEEK STUDY IN RATS

Groups of 10 male and 10 female F344/N rats were exposed to 0, 500, 1,000, 2,000, 4,000, or 8,000 ppm isobutyraldehyde by inhalation, 6 hours per day, 5 days a week, for 13 weeks. All rats exposed to 8,000 ppm died before the end of the study. Three male rats and six female rats in the 4,000 ppm groups and one female in the 500 ppm group died before the end of the study. The final mean body weight of male rats in the 4,000 ppm group and the body weight gains of 4,000 ppm males and females were significantly less than those of the chamber controls. Clinical findings in rats exposed to 4,000 or 8,000 ppm included abnormal respiratory sounds, decreased activity, nasal discharge, prostration, and slowed respiration. A minimal mature neutrophilia, evidenced by increased segmented neutrophil numbers, occurred in exposed groups of male and female rats. Exposure to isobutyraldehyde resulted in minimal increases in alanine aminotransferase activity in

all groups of male and female rats. Spermatozoal motility in 500 and 1,000 ppm males was significantly reduced and females exposed to 4,000 ppm differed significantly from the chamber control females in the relative time spent in the estrous stages.

No gross lesions were observed at necropsy that could be associated with isobutyraldehyde exposure. In the 8,000 ppm groups, severe necrosis of the epithelium, and occasionally of the entire mucosa, of the nasal turbinates accompanied by an acute inflammatory reaction was observed. Increased incidences of squamous metaplasia and mild acute inflammation occurred in male and female rats exposed to 4,000 ppm. Minimal to mild degeneration of the olfactory epithelium was observed in all male rats in the 2,000 and 4,000 ppm groups. Male rats exposed to 4,000 or 8,000 ppm and females exposed to 4,000 ppm had mild osteodystrophy of the turbinate bone. The incidences of necrosis/degeneration of the larynx and trachea were increased in male rats in the 8,000 ppm group. The incidences of mild to moderate lymphoid depletion of the spleen and thymus and lymphoid necrosis of the thymus were significantly increased in male and female rats exposed to 8,000 ppm.

13-WEEK STUDY IN MICE

Ten male and 10 female B6C3F$_1$ mice were exposed to 0, 500, 1,000, 2,000, 4,000, or 8,000 ppm isobutyraldehyde by inhalation, 6 hours per day, 5 days per week, for 13 weeks. One male in the chamber control group, one male in the 1,000 ppm group, nine males and all females in the 4,000 ppm groups, and all males and females in the 8,000 ppm groups died before the end of the study. The final mean body weight and body weight gain of female mice in the 1,000 ppm group were significantly less than those of the chamber controls. Clinical findings included decreased activity, tremors, prostration, and slower and labored respiration. The absolute and relative kidney weights of males in the 1,000 and 2,000 ppm groups were significantly increased.

There were no gross lesions observed at necropsy that could be associated with isobutyraldehyde exposure. Histopathologically, the nasal cavity and lymphopoietic tissues were considered target organs, with changes similar, but not identical, to those observed in rats. Increased incidences of nonneoplastic lesions of the nasal cavity were observed in male and female mice exposed to 1,000 ppm or greater. These lesions included necrosis, inflammation, hyperplasia, and squamous metaplasia of the epithelium; serous and suppurative exudate within the nasal passages; olfactory epithelial degeneration; and osteodystrophy of the turbinate bone. Mild to moderate lymphoid depletion and/or lymphoid necrosis were observed in the thymus of male and female mice exposed to 8,000 ppm.

2-YEAR STUDY IN RATS

Groups of 50 male and 50 female F344/N rats were exposed to 0, 500, 1,000, or 2,000 ppm isobutyraldehyde by inhalation, 6 hours per day, 5 days per week, for 105 weeks.

Survival and Body Weights

No differences in survival rates between exposed and chamber control rats were found. The mean body weights of male and female rats were generally similar to those of the chamber controls throughout the study.

Pathology Findings

No increase in neoplasm incidences that could be attributed to exposure to isobutyraldehyde was observed in male or female rats. Nonneoplastic lesions related to isobutyraldehyde exposure were limited to the nose and consisted of squamous metaplasia of the respiratory epithelium, degeneration of the olfactory epithelium, and suppurative inflammation. Incidences of minimal to mild squamous metaplasia in 1,000 and 2,000 ppm males and females and in 500 ppm females were significantly greater than those in the chamber controls. Another lesion associated with isobutyraldehyde exposure was minimal to mild degeneration of the olfactory epithelium in 2,000 ppm males and females. The incidences of suppurative inflammation (rhinitis) in male and female rats exposed to 2,000 ppm were increased compared to the chamber controls.

2-YEAR STUDY IN MICE

Groups of 50 male and 50 female B6C3F$_1$ mice were exposed to 0, 500, 1,000, or 2,000 ppm

isobutyraldehyde by inhalation, 6 hours per day, 5 days per week, for 105 weeks.

Survival and Body Weights

There was an exposure-related decrease in survival of male mice, and the survival of males exposed to 2,000 ppm was marginally lower than that of the chamber controls. The mean body weights of female mice exposed to 1,000 or 2,000 ppm were lower than those of the chamber controls during the second year of the study.

Pathology Findings

No neoplasms that could be attributed to isobutyraldehyde exposure were observed in mice. Nonneoplastic lesions related to isobutyraldehyde exposure were limited to the nose. The incidences of olfactory epithelial degeneration in 1,000 and 2,000 ppm males and females were significantly greater than in the chamber controls.

GENETIC TOXICOLOGY

Isobutyraldehyde is mutagenic *in vitro* and *in vivo*, with the strongest responses observed in mammalian cell assays that measured chromosomal damage. Results of an initial mutagenicity test in *S. typhimurium* were negative; a second test, conducted with different strains and varying concentrations of induced S9 activation enzymes, gave equivocal results. Strongly positive responses were obtained in the mouse lymphoma assay for mutation induction in L5178Y cells without S9 and in cytogenetic tests for induction of sister chromatid exchanges and chromosomal aberrations in cultured Chinese hamster ovary cells. Sister chromatid exchanges were significantly increased with and without S9, but induction of chromosomal aberrations was noted unequivocally only in the absence of S9. No induction of sex-linked recessive lethal mutations was observed in germ cells of male *D. melanogaster* administered isobutyraldehyde by feeding or by injection.

In vivo, isobutyraldehyde was demonstrated to induce chromosomal aberrations in bone marrow cells of male mice, but no increases in micronuclei were observed in bone marrow cells of mice or rats after administration of isobutyraldehyde. All these *in vivo* cytogenetic studies used doses that reached lethality.

CONCLUSIONS

Under the conditions of these 2-year inhalation studies, there was *no evidence of carcinogenic activity** of isobutyraldehyde in male or female F344/N rats or male or female B6C3F$_1$ mice exposed to 500, 1,000, or 2,000 ppm.

In male and female rats, exposure to isobutyraldehyde induced squamous metaplasia and suppurative inflammation of the nasal respiratory epithelium and degeneration of the nasal olfactory epithelium. In male and female mice, exposure to isobutyraldehyde caused degeneration of the nasal olfactory epithelium.

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* Explanation of Levels of Evidence of Carcinogenic Activity is on page 9. A summary of the Technical Reports Review Subcommittee comments and the public discussion on this Technical Report appears on page 11.

Summary of the 2-Year Carcinogenesis and Genetic Toxicology Studies of Isobutyraldehyde

	Male F344/N Rats	Female F344/N Rats	Male $B6C3F_1$ Mice	Female $B6C3F_1$ Mice
Concentrations in air	Chamber control, 500, 1,000, or 2,000 ppm	Chamber control, 500, 1,000, or 2,000 ppm	Chamber control, 500, 1,000, or 2,000 ppm	Chamber control, 500, 1,000, or 2,000 ppm
Body weights	Exposed groups similar to chamber control groups	Exposed groups similar to chamber control groups	Exposed groups similar to chamber control groups	1,000 and 2,000 ppm groups less than chamber control groups
Survival rates	12/50, 15/50, 11/50, 10/50	27/50, 24/50, 24/50, 32/50	40/50, 37/50, 35/50, 30/50	28/50, 32/50, 36/50, 37/50
Nonneoplastic effects	Nose: respiratory epithelium squamous metaplasia (1/50, 1/49, 10/49, 44/50); suppurative inflammation (5/50, 3/49, 6/49, 15/50); olfactory epithelium degeneration (0/50, 0/49, 3/49, 44/50)	Nose: respiratory epithelium squamous metaplasia (1/49, 11/50, 9/49, 44/50); suppurative inflammation (2/49, 3/50, 5/49, 11/50); olfactory epithelium degeneration (0/49, 0/50, 2/49, 45/50)	Nose: olfactory epithelium degeneration (0/50, 0/50, 11/50, 45/50)	Nose: olfactory epithelium degeneration (1/50, 1/50, 27/50, 49/50)
Neoplastic effects	None	None	None	None
Level of evidence of carcinogenic activity	No evidence	No evidence	No evidence	No evidence
Genetic toxicology				
Salmonella typhimurium gene mutations:	Negative in strains TA97, TA98, TA100, TA102, TA1535, and TA1537 with and without S9; equivocal in strain TA104 with S9			
Mouse lymphoma gene mutations:	Positive without S9			
Sister chromatid exchanges				
Cultured Chinese hamster ovary cells *in vitro*:	Positive with and without S9			
Chromosomal aberrations				
Cultured Chinese hamster ovary cells *in vitro*:	Positive without S9			
Mouse bone marrow *in vivo*:	Positive			
Sex-linked recessive lethal mutations				
Drosophila melanogaster:	Negative			
Micronucleated erythrocytes				
Mouse bone marrow *in vivo*:	Negative			
Rat bone marrow *in vivo*:	Negative			

EXPLANATION OF LEVELS OF EVIDENCE OF CARCINOGENIC ACTIVITY

The National Toxicology Program describes the results of individual experiments on a chemical agent and notes the strength of the evidence for conclusions regarding each study. Negative results, in which the study animals do not have a greater incidence of neoplasia than control animals, do not necessarily mean that a chemical is not a carcinogen, inasmuch as the experiments are conducted under a limited set of conditions. Positive results demonstrate that a chemical is carcinogenic for laboratory animals under the conditions of the study and indicate that exposure to the chemical has the potential for hazard to humans. Other organizations, such as the International Agency for Research on Cancer, assign a strength of evidence for conclusions based on an examination of all available evidence, including animal studies such as those conducted by the NTP, epidemiologic studies, and estimates of exposure. Thus, the actual determination of risk to humans from chemicals found to be carcinogenic in laboratory animals requires a wider analysis that extends beyond the purview of these studies.

Five categories of evidence of carcinogenic activity are used in the Technical Report series to summarize the strength of the evidence observed in each experiment: two categories for positive results (**clear evidence** and **some evidence**); one category for uncertain findings (**equivocal evidence**); one category for no observable effects (**no evidence**); and one category for experiments that cannot be evaluated because of major flaws (**inadequate study**). These categories of interpretative conclusions were first adopted in June 1983 and then revised in March 1986 for use in the Technical Report series to incorporate more specifically the concept of actual weight of evidence of carcinogenic activity. For each separate experiment (male rats, female rats, male mice, female mice), one of the following five categories is selected to describe the findings. These categories refer to the strength of the experimental evidence and not to potency or mechanism.

- **Clear evidence** of carcinogenic activity is demonstrated by studies that are interpreted as showing a dose-related (i) increase of malignant neoplasms, (ii) increase of a combination of malignant and benign neoplasms, or (iii) marked increase of benign neoplasms if there is an indication from this or other studies of the ability of such tumors to progress to malignancy.
- **Some evidence** of carcinogenic activity is demonstrated by studies that are interpreted as showing a chemical-related increased incidence of neoplasms (malignant, benign, or combined) in which the strength of the response is less than that required for clear evidence.
- **Equivocal evidence** of carcinogenic activity is demonstrated by studies that are interpreted as showing a marginal increase of neoplasms that may be chemical related.
- **No evidence** of carcinogenic activity is demonstrated by studies that are interpreted as showing no chemical-related increases in malignant or benign neoplasms.
- **Inadequate study** of carcinogenic activity is demonstrated by studies that, because of major qualitative or quantitative limitations, cannot be interpreted as valid for showing either the presence or absence of carcinogenic activity.

When a conclusion statement for a particular experiment is selected, consideration must be given to key factors that would extend the actual boundary of an individual category of evidence. Such consideration should allow for incorporation of scientific experience and current understanding of long-term carcinogenesis studies in laboratory animals, especially for those evaluations that may be on the borderline between two adjacent levels. These considerations should include:

- adequacy of the experimental design and conduct;
- occurrence of common versus uncommon neoplasia;
- progression (or lack thereof) from benign to malignant neoplasia as well as from preneoplastic to neoplastic lesions;
- some benign neoplasms have the capacity to regress but others (of the same morphologic type) progress. At present, it is impossible to identify the difference. Therefore, where progression is known to be a possibility, the most prudent course is to assume that benign neoplasms of those types have the potential to become malignant;
- combining benign and malignant tumor incidence known or thought to represent stages of progression in the same organ or tissue;
- latency in tumor induction;
- multiplicity in site-specific neoplasia;
- metastases;
- supporting information from proliferative lesions (hyperplasia) in the same site of neoplasia or in other experiments (same lesion in another sex or species);
- presence or absence of dose relationships;
- statistical significance of the observed tumor increase;
- concurrent control tumor incidence as well as the historical control rate and variability for a specific neoplasm;
- survival-adjusted analyses and false positive or false negative concerns;
- structure-activity correlations; and
- in some cases, genetic toxicology.

NATIONAL TOXICOLOGY PROGRAM BOARD OF SCIENTIFIC COUNSELORS
TECHNICAL REPORTS REVIEW SUBCOMMITTEE

The members of the Technical Reports Review Subcommittee who evaluated the draft NTP Technical Report on isobutyraldehyde on 12 December 1996 are listed below. Subcommittee members serve as independent scientists, not as representatives of any institution, company, or governmental agency. In this capacity, subcommittee members have five major responsibilities in reviewing the NTP studies:

- to ascertain that all relevant literature data have been adequately cited and interpreted,
- to determine if the design and conditions of the NTP studies were appropriate,
- to ensure that the Technical Report presents the experimental results and conclusions fully and clearly,
- to judge the significance of the experimental results by scientific criteria, and
- to assess the evaluation of the evidence of carcinogenic activity and other observed toxic responses.

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SUMMARY OF TECHNICAL REPORTS REVIEW SUBCOMMITTEE COMMENTS

On 12 December 1996, the draft Technical Report on the toxicology and carcinogenesis studies of isobutyraldehyde received public review by the National Toxicology Program's Board of Scientific Counselors' Technical Reports Review Subcommittee. The review meeting was held at the National Institute of Environmental Health Sciences, Research Triangle Park, NC.

Dr. K.M. Abdo, NIEHS, introduced the toxicology and carcinogenesis studies of isobutyraldehyde by discussing the uses of the chemical and the rationale for study, describing the experimental design, reporting on survival and body weight effects, and commenting on compound-related nonneoplastic lesions in rats and mice. The proposed conclusions for the 2-year studies were *no evidence of carcinogenic activity* in male or female F344/N rats or $B6C3F_1$ mice.

Dr. Tyson, a principal reviewer, agreed with the proposed conclusions. He suggested adding a discussion of the possible reasons for the discrepancy between genotoxicity reported in previous studies and the NTP studies (page 50).

Dr. Brown, the second principal reviewer, agreed with the proposed conclusions. He suggested that the portion of the Results section regarding the insignificance of the nasal tumors found in rats be included in the Discussion and Conclusions section in view of the rarity of nasal neoplasms of any kind. Dr. Brown acknowledged the appropriateness of the inhalation route. He also noted that significant human exposure can occur from food or water and that a comment on the natural availability of the compound would be helpful. Dr. Abdo replied that when added to food or water, the chemical is conjugated by or combines with other chemicals and some degradation of the isobutyraldehyde is observed. Further, he added, isobutyraldehyde was nominated for study due to concerns of worker exposure to the chemical.

Dr. Tyson moved that the Technical Report on isobutyraldehyde be accepted with the revisions discussed and the conclusions as written for male and female rats and mice, *no evidence of carcinogenic activity*. Dr. Brown seconded the motion, which was accepted unanimously with eight votes.